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Development and Research on the cognitive-enhancing effects of Chinese herbs

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智能障礙
Cognitive dysfunction

1. WHO reported that when aged people (**older than 65**) is over 7 percentage of all people, it is called **aging country**.

2. Dementia is the most common disease (**about 5 percentage**) happened in aged people.

Clinical symptoms of dementia

1.Deterioration of cognition

2.Early phase: Loss of recent memory

3.**Late phase**: **forgotten the learned experience**

Classification of amnesia

1. **Anterograde amnesia** is a symptom that the learned experience a moment ago was forgotten, and occurred in **presenile dementia**
2. **Retrograde amnesia** is a symptom that the learned experience long time ago was forgotten, and occurred in **late phase of Alzheimer's disease**

進行性健忘動物模式

Animal Models of Anterograde Amnesia

1. Animal models of **anterograde amnesia** are established by chemicals described as followed
   (1) **Scopolamine** induce **anterograde amnesia** by blocking cholinergic muscarinic receptors
   (2) **p-Chloroamphetamine** induce **anterograde amnesia** by promoting the release of serotonin

退行性健忘動物模式

Animal Models of Retrograde Amnesia

2. Animal models of **retrograde amnesia** are established by chemicals described as followed
   (1) **Cycloheximide** induce **retrograde amnesia** by inhibiting the protein synthesis
   (2) **Apomorphine** induce **retrograde amnesia** by activating dopaminergic receptors

Classification of Cognitive enhancers

- There are three types in cognitive enhancers
  1. Vasodilators：**Hydergine**
  2. Acetylcholinesterase inhibitors：**Huperzine-A**
  3. Nootropics：**Piracetam**

  Their clinical efficacy is slight and they have more side effects including **headache, dizziness** et al..
- Therefore, we develop new cognitive enhancers from Chinese herbs evaluated by **passive avoidance learning** and **water maze**

記憶神經生化機制
Neurobiochemical Mechanism of Memory

(Jodar & Kaneto, Jpn J Pharmacol, 1995)

- Related neurotransmitters in memory formation included
  1. **Acetylcholine**
  2. **Serotonin**
  3. **Dopamine**
- Furthermore, these above neurotransmitter stimulate the activities of postsynapyic protein kinase and then promote the increase in **protein synthesis**.

Classification of Memory Processes

1、 Learning acquisition

2、 Memory storage

3、 Memory retrieval

4、 Reacquisition、Rehearsal

5、 Forget

Learning Acquisition & Scopolamine

(Elord et al., Pharmacol Biochem Behav, 1988)

🕮 **Scopolamine** is a cholinergic muscarinic antagonist and decreases the central cholinergic activity.

🕮 **Scopolamine** impairs learning acquisition and induces anterograde amnesia.

Classification of animal learning models

(Graham, Psychological Psychology, 1990)

Animal learning models are usually classified into these below groups by reinforcers

1. **8-radial arm maze** is established by positive reinforcers such as food and belongs to **rewarded memory**
2. **Water maze** is established by negative reinforcers such as water and belongs to **aversive memory** and **spatial memory**
3. **Active avoidance** is established by negative reinforcers such as footshock, and belongs to **aversive memory** and **associative memory**
4. **Passive avoidance** is established by negative reinforcers such as footshock, and belongs to **aversive memory**

Passive Avoidance Learning

(Worms et al., Psychopharmacology, 1989)

📖 **Adaptive period**

1 day before the training trial, the rats stay at the experimental room for 2 hrs and then at the dark compartment for 10 sec

📖 **Training period**

First, each rat was placed in the light compartment with its back to the guillotine door. Once the rat entered the dark compartment, the door was closed. An inescapable scrambled footshock (1.0 mA for 2 sec) was then delivered.

Passive Avoidance Learning

(Worms et al., Psychopharmacology, 1989)

📖 **Retention period**

The retention trial was carried out 24 hr later. The rat was once again placed in the light compartment and as in the case of the training trial, the guillotine door was opened and the step-through latency (STL) was recorded and used as a measure of retention. An upper cut-off time of 300 sec was set.

Effects of Cognitive-enhancing Chinese Herbs on scopolamine-induced Acquisition dysfunction

中藥名稱	植物學名	改善效果
人參	*Panax ginseng*	+++
天麻	*Gastrodia elata*	+++
地黃	*Rehmannia glutinosa*	++
牛膝	*Achyranthes bidentata*	++
五味子	*Schisandra chinensis*	++
蛇床子	*Cnidium monnieri*	++
石菖蒲	*Acorus gramineus*	++
三七	*Panax notoginseng*	++
黃連	*Coptis chinensis*	+

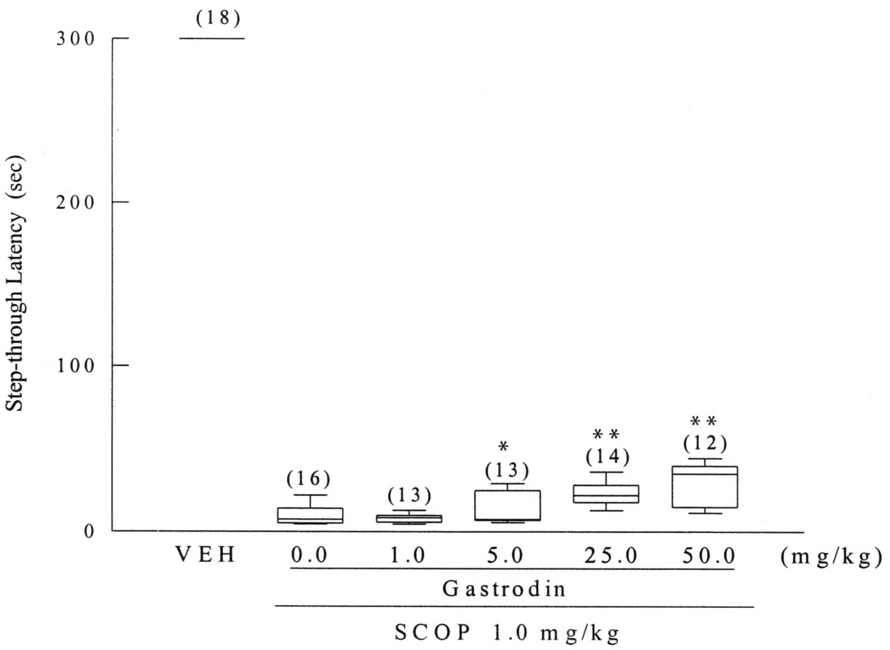
We got the result that the attenuating effects of *Gastrodia elata* on scopolamine-induced learning impairment were best than the other Chinese herbs.

Effects of Cognitive-enhancing Chinese Herbs on scopolamine-induced Acquisition dysfunction

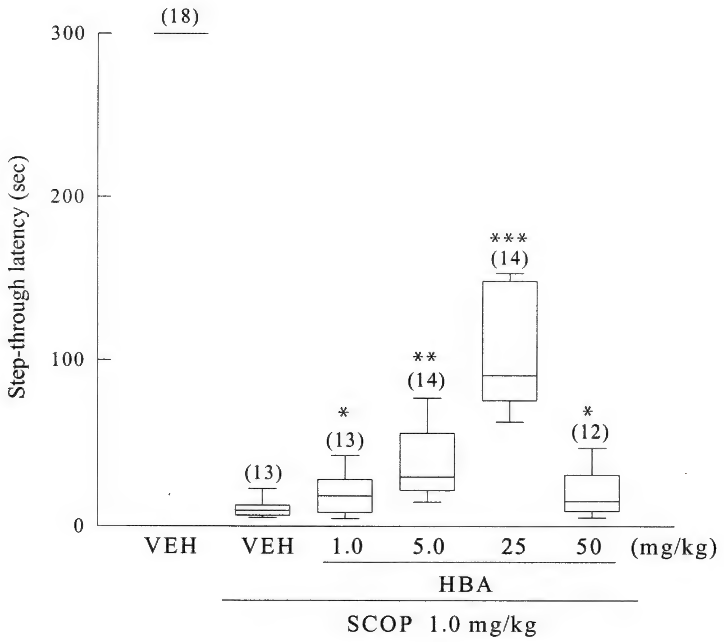
中藥名稱	植物學名	改善效果
丹參	*Salvia miltiorrhiza*	—
香附	*Cyperus rotundus*	—
何首烏	*Polygonum multiflorum*	—
補骨脂	*Psoralea corylifolia*	—
薯蕷	*Dioscorea opposita*	—
麥門冬	*Ophiopogon japonicus*	—
知母	*Anemarrhena asphodeloide*	—

Isolation of Active Constituents

- **Gastrodin** was isolated from the *n*-butanolic layer of methanolic extract of Tianma.
- ***p*-Hydroxybenzyl alcohol** was isolated from the ethylacetate layer of methanolic extract of Tianma.



This slide shows that gastrodin at 5 mg/kg could prolong the STL shortened by SCOP.



This slide shows that HBA at 1 mg/kg prolonged the STL shortened by SCOP.

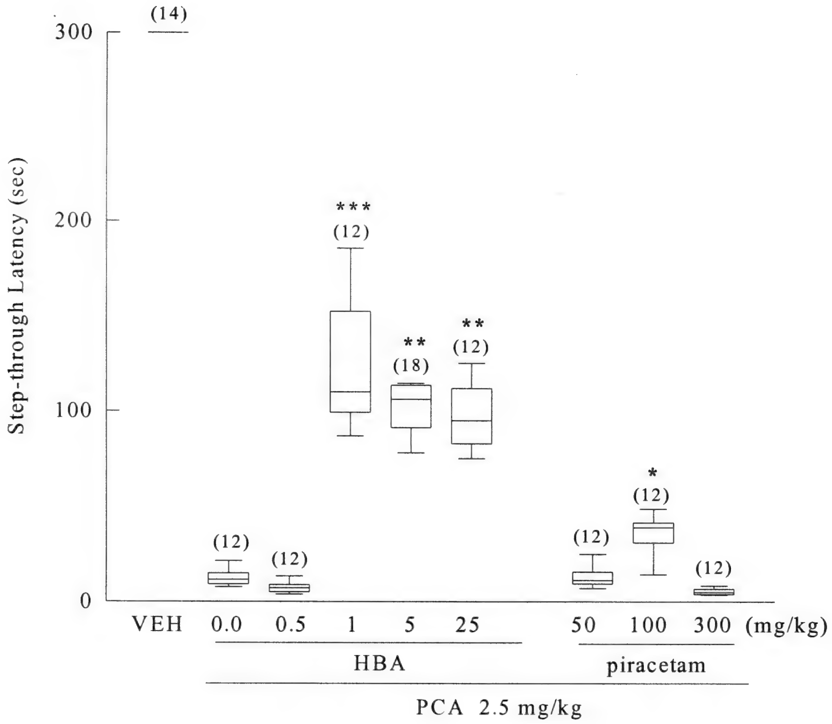
Conclusion（1）

- The major active constituents of Tianma are **gastrodin** and ***p*-hydroxybenzyl alcohol**
- The effect of ***p*-hydroxybenzyl alcohol** is better than that of **gastrodin**.

Learning Acquisition & *p*-Chloroamphetamine

(Ogren, Brain Res Bull, 1986)

- ***p*-Chloroamphetamine** is a serotonergic releaser and increases the central serotonergic activity.
- ***p*-Chloroamphetamine** impairs learning acquisition and induces anterograde amnesia.

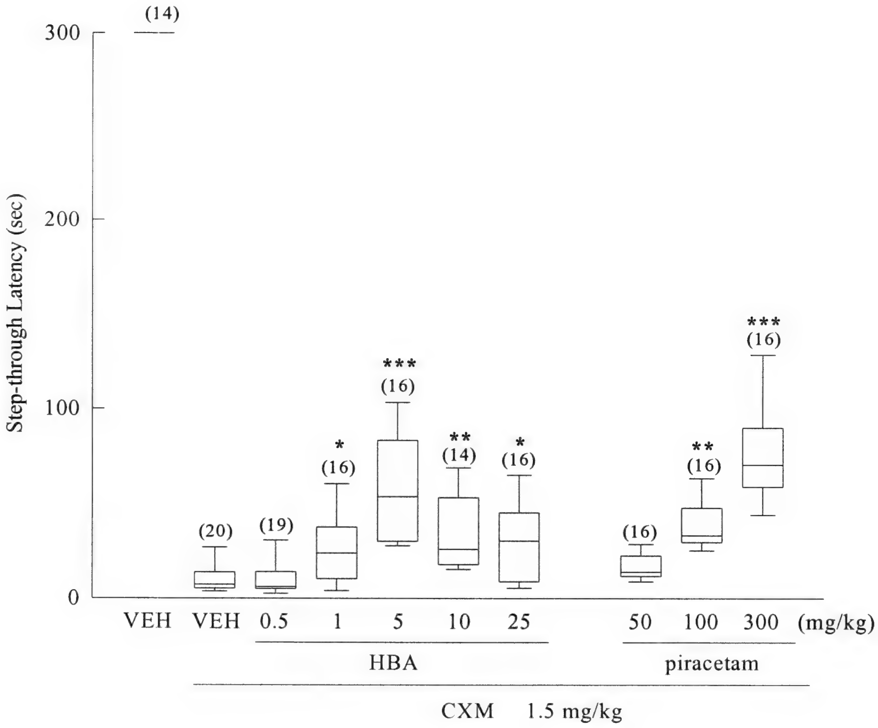


This slide shows that HBA at 1 mg/kg prolonged the STL shortened by PCA. Its effect was more potency than that of piracetam.

Memory Consolidation & Cycloheximide

(Davis, Psychology Bulletin, 1984)

- **Cycloheximide** is protein synthesis inhibitor via inhibiting the translation process of mRNA.
- **Cycloheximide** inhibits about 80%protein synthesis, and impairs memory consolidation and long-term memory.

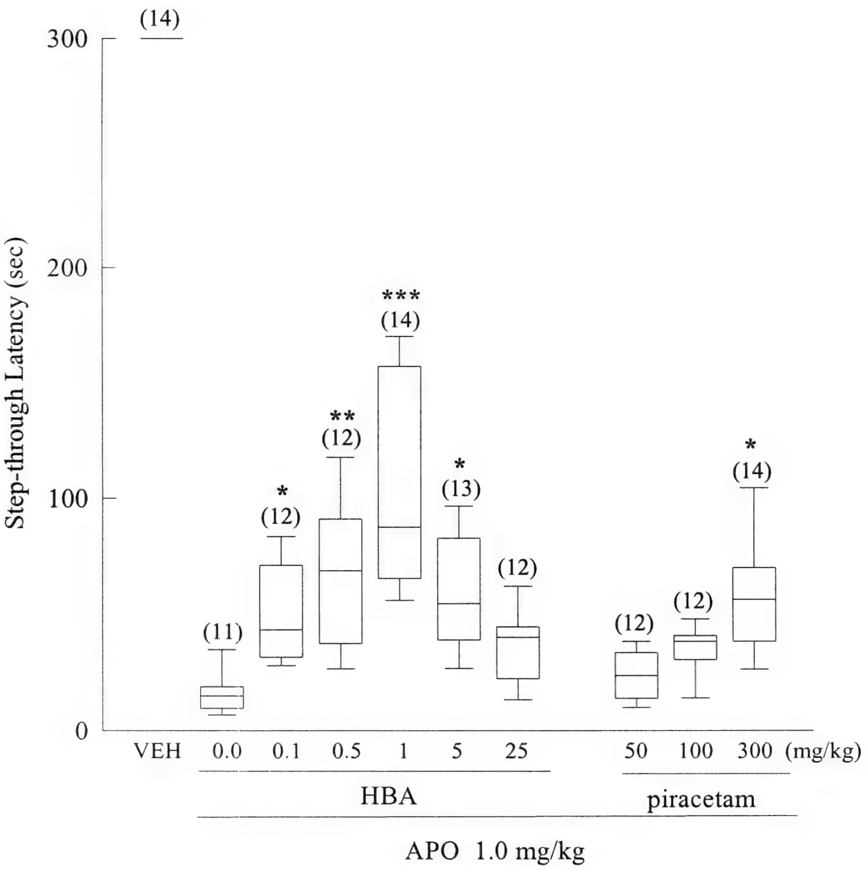


This slide shows that HBA at 1 mg/kg prolonged the STL shortened by CXM. Its effect was more potency than that of piracetam.

Memory retrieval & Apomorphine

(Ichihara et al., Pharmacol Biochem Behav, 1988)

1. At low dosage（0.1 mg/kg），**apomorphine** belongs to a dopamine autoreceptor agonist and enhances learning performance via decreasing the release of dopamine
2. At high dosage（1.0 mg/kg），**apomorphine** belongs to a postsynaptic dopaminergic agonist and impairs memory retrieval dysfunction via activating dopaminergic activity



This slide shows that HBA at 0.1 mg/kg prolonged the STL shortened by APO. Its effect was more potency than that of piracetam.

Conclusion（2）

- ***p*-Hydroxybenzyl alcohol** attenuated the scopolamine-induced acquisition impairment, cycloheximide-induced storage impairment and apomorphine-induced retrieval impairment
- The potency of ***p*-hydroxybenzyl alcohol** on counteracting the memory dysfunction was better than that of **piracetam**

Group	Dose (g/kg)	STL (sec)
Vehicle		> 300
SCOP		17.2± 0.3
SCOP-treated		
Ginseng	0.5	48.8± 7.5*
	1	122.5± 12.4**
Tianma	0.5	26.9± 6.7
	1	86.1± 13.3**
Ginseng (0.5) plus Tianma (0.5)		187.4± 10.2***

This slide shows that **Ginseng** plus **Tianma** could prolong the STL shortened by SCOP, and this effect was better than each other.

Prescriptions of Cognition- Enhancing Chinese herbs

🕮 Prescriptions of cognitive-enhancing Chinese herbs include

1. **Pu-Chung-I-Chi-Tang**（補中益氣湯，Invigorating vital energy）
2. **Tien-Wang-Pu-Hsin-Dang**（天王補心丹，Invigorating Yin）
3. **Gui-Pi-Tang**（歸脾湯，Invigorating hemostatics）
4. **LiuWei Dihuang Wang**(六味地黃丸，Invigorating Yang）

Group	Dose (g/kg)	STL (sec)
Saline		＞300
SCOP		17.2± 0.3
SCOP + Prescriptions		
Pu-Chung-I-Chi-Tang 〈補中益氣湯〉	0.1	16.5± 0.2
	1	183.6± 9.6***
Gui-Pi-Tang 〈歸脾湯〉	0.1	18.3± 2.3
	1	47.8± 4.0**
Tien-Wang-Pu-Hsin-Dang 〈天王補心丹〉	0.1	78.6± 5.1**
	1	184.7± 17.8***
LiuWei Dihuang Wang 〈六味地黃丸〉	0.1	36.8± 4.2*
	1	142.5± 13.5***

This slide shows that all prescriptions of Chinese herbs attenuated the impairment of learning acquisition induced by **SCOP**.

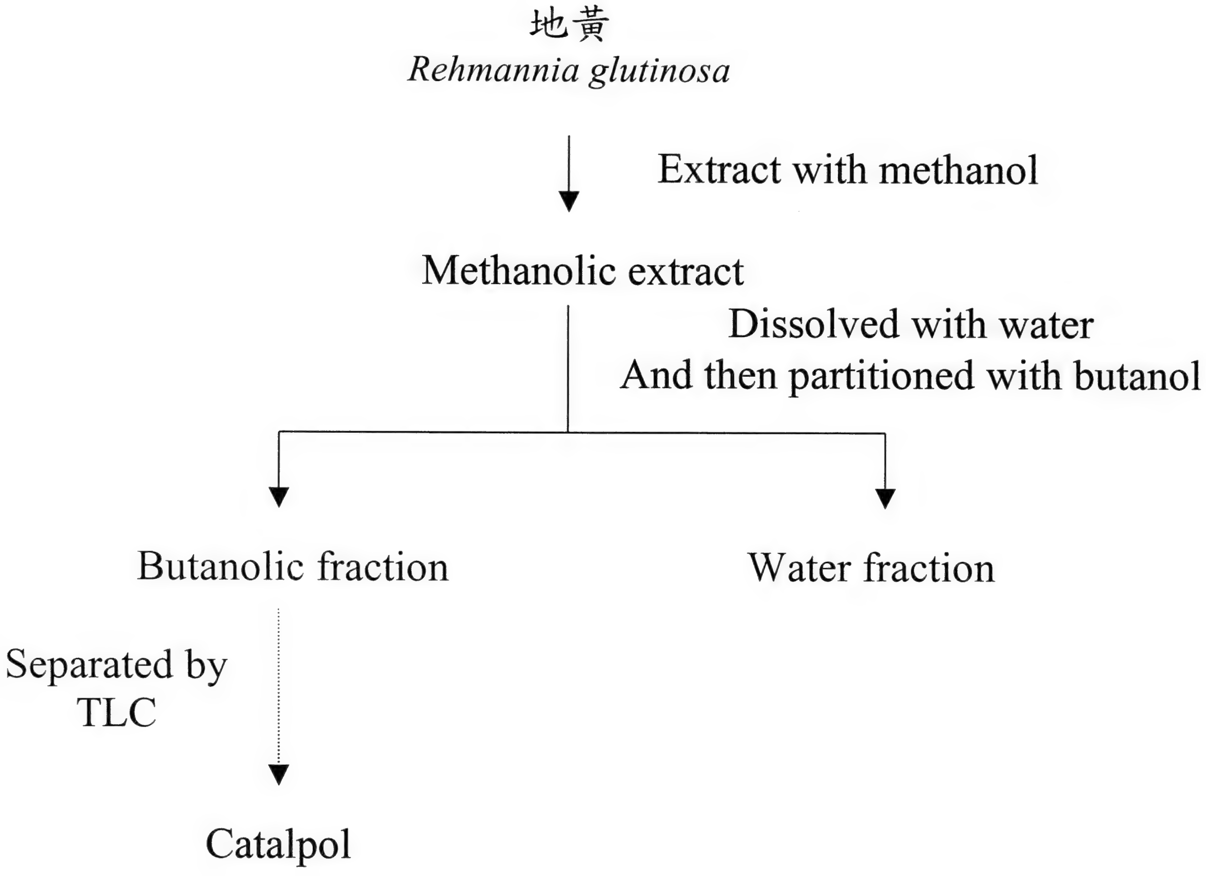
Group	Dose (g/kg)	STL (sec)
Saline		＞300
CXM		13.2± 0.6
CXM plus prescriptions		
Pu-Chung-I-Chi-Tang 〈補中益氣湯〉	0.1	16.5± 0.2
	1	66.6± 1.1**
Gui-Pi-Tang 〈歸脾湯〉	0.1	101.4± 3.8***
	1	198.8± 2.5***
Tien-Wang-Pu-Hsin-Dang 〈天王補心丹〉	0.1	75.8± 5.7**
	1	162.7± 15.9***
LiuWei Dihuang Wang 〈六味地黃丸〉	0.1	58.6± 8.7**
	1	136.9± 10.8***

This slide shows that all prescriptions of Chinese herbs attenuated the impairment of memory consolidation induced by **CXM**.

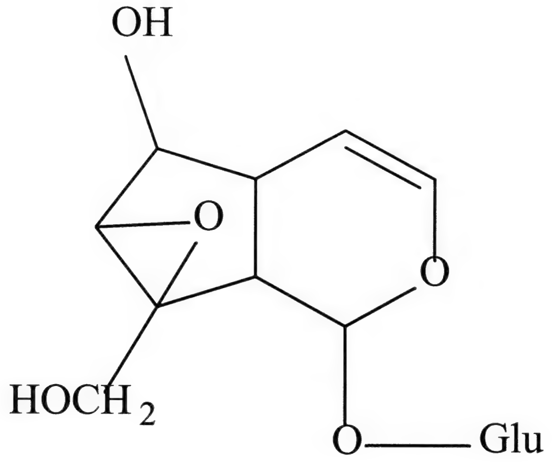
Conclusion（3）

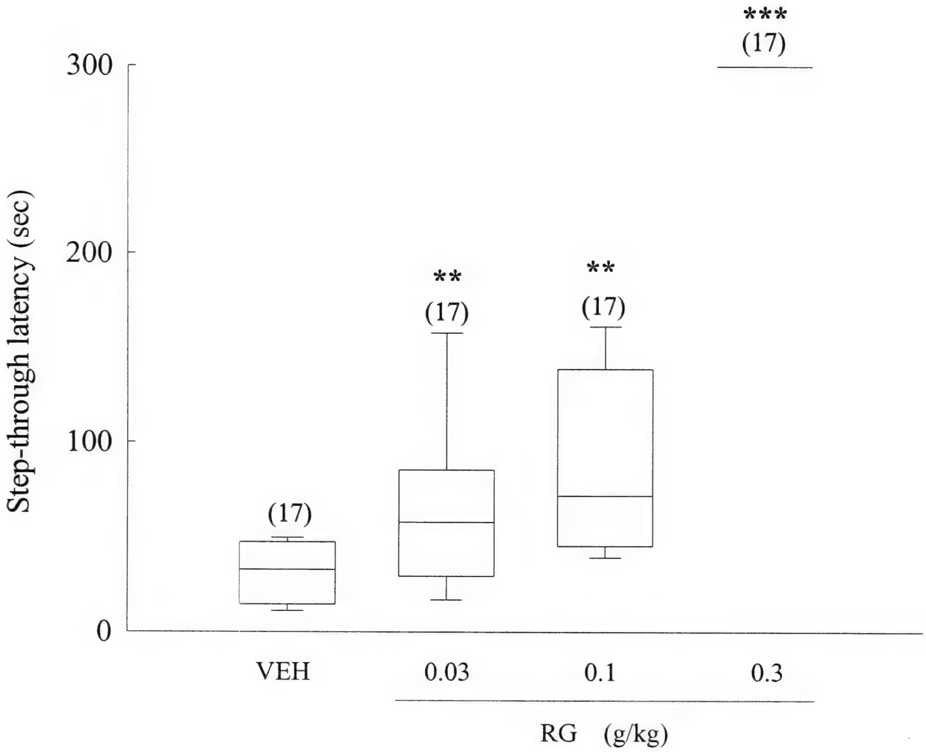
Prescriptions	Facilitatory effect on Memory processes	Preventive Effects
Pu-Chung-I-Chi-Tang 〈補中益氣湯〉	Learning acquisition	Anterograde amnesia
Gui-Pi-Tang〈歸脾湯〉	Memory storage	Retrograde amnesia
Tien-Wang-Pu-Hsin-Dang 〈天王補心丹〉	Learning acquisition Memory storage	Anterograde amnesia Retrograde amnesia
LiuWei Dihuang Wang 〈六味地黃丸〉	Learning acquisition Memory storage	Anterograde amnesia Retrograde amnesia

Isolation of Active Constituents

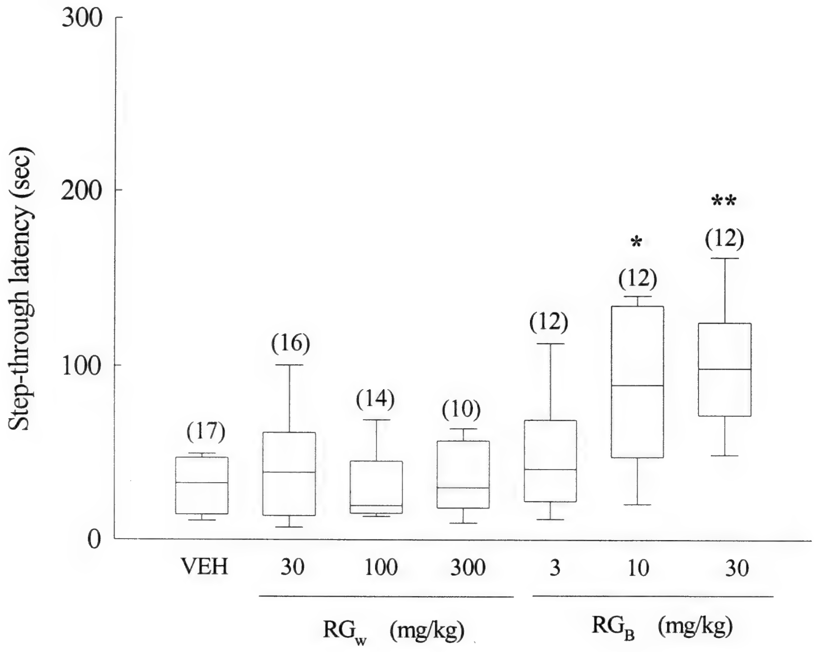


Structure of Catalpol





This slide shows that methanolic extract of *Rehmannia glutinosa* facilitated the passive avoidance performance in rats.



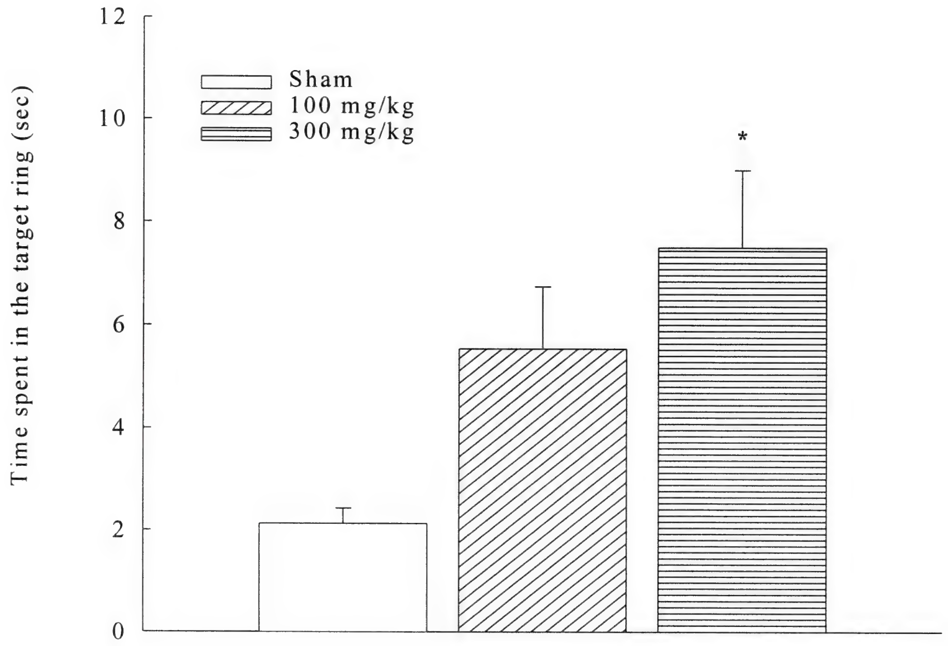
This slide shows that butanolic layer of *Rehmannia glutinosa* facilitated the passive avoidance performance in rats.

Water maze

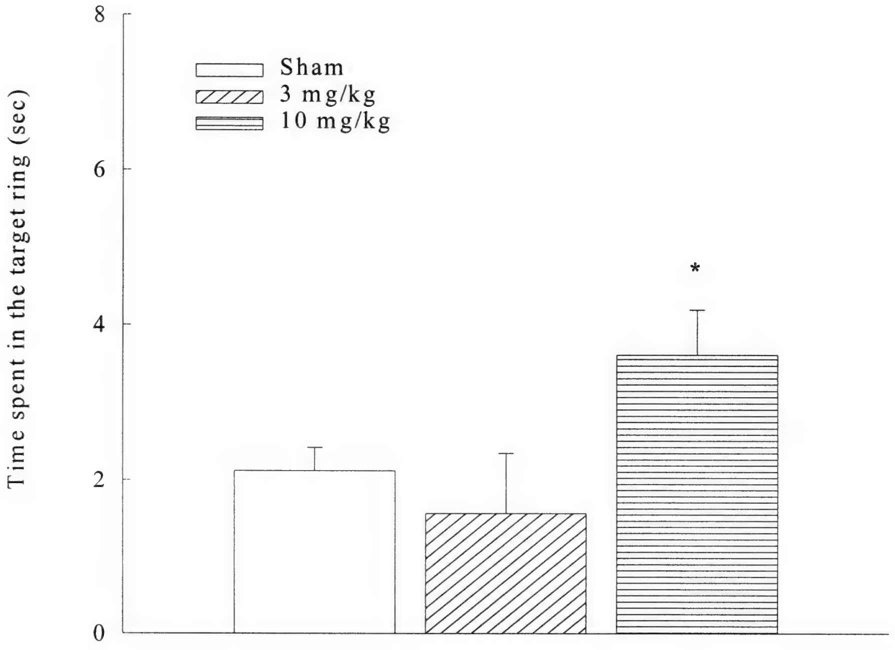
1. We used the **Morris water maze**, comprised a circular water-bath whose and a platform, to evaluate the orientation and spatial memory
2. All rats were trained four consecutive trials per day for three days. Rats were given up to 120 sec to swim and find the platform.

Water maze

3. Performance of water maze are classified into two types:
   (1). **Spatial performance**〈空間操作〉, which the platform was put 1 cm below the water surface, is evaluated four consecutive trials per day from 1 to 3 days
   (2). **Reference memory**〈參考記憶〉, which the platform was removed, is evaluated on 4 hours after 3 consecutive training days
4. The time taken to reach the platform was measured



This slide shows that methanolic extract of *Rehmannia glutinosa* at 300 mg/kg facilitate reference memory on 4 hours after 3 consecutive training days in rats.



This slide shows that catalpol at 10 mg/kg facilitated reference memory on 4 hours after 3 consecutive training days in rats.

痴呆動物模式

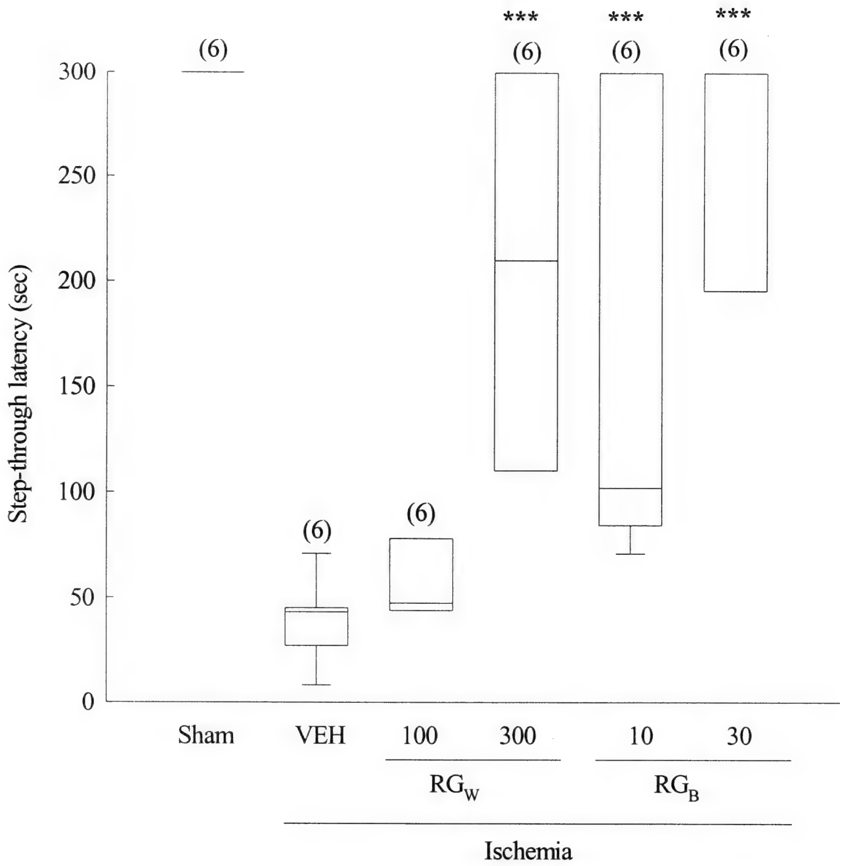
Animal Models of Dementia

1. Animal model of **cerebral vascular dementia** is established by bilateral carotid artery occlusion

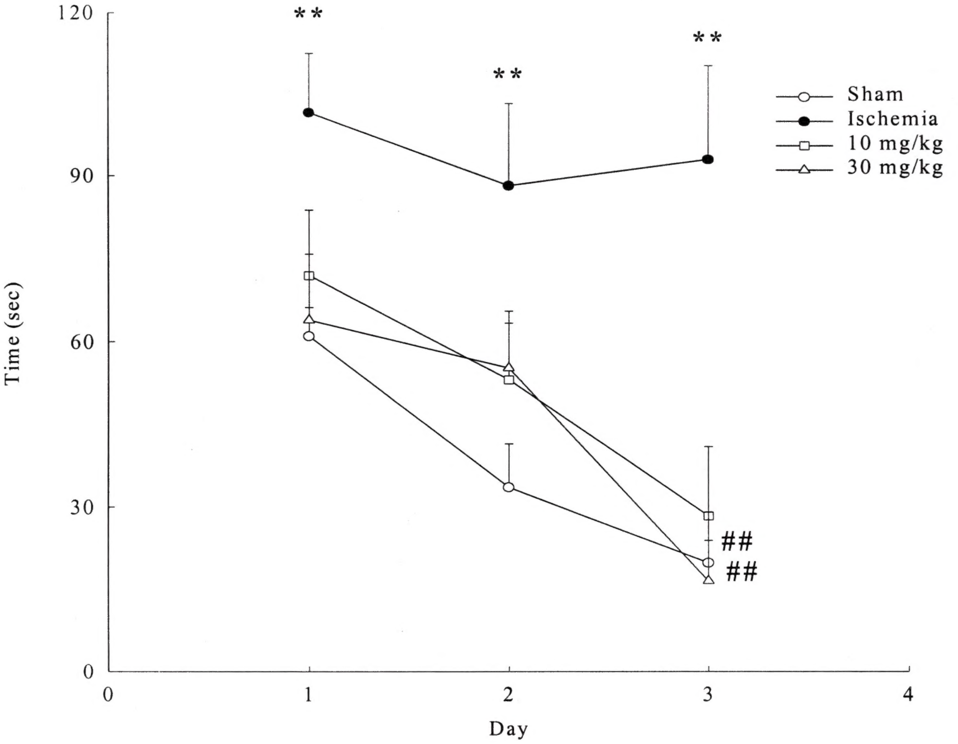
   （Caldwell et al., Brain Res. 1997）

2. Animal model of **senile dementia** is established by intracisteral infusion of Amyloid β peptide (1-40)

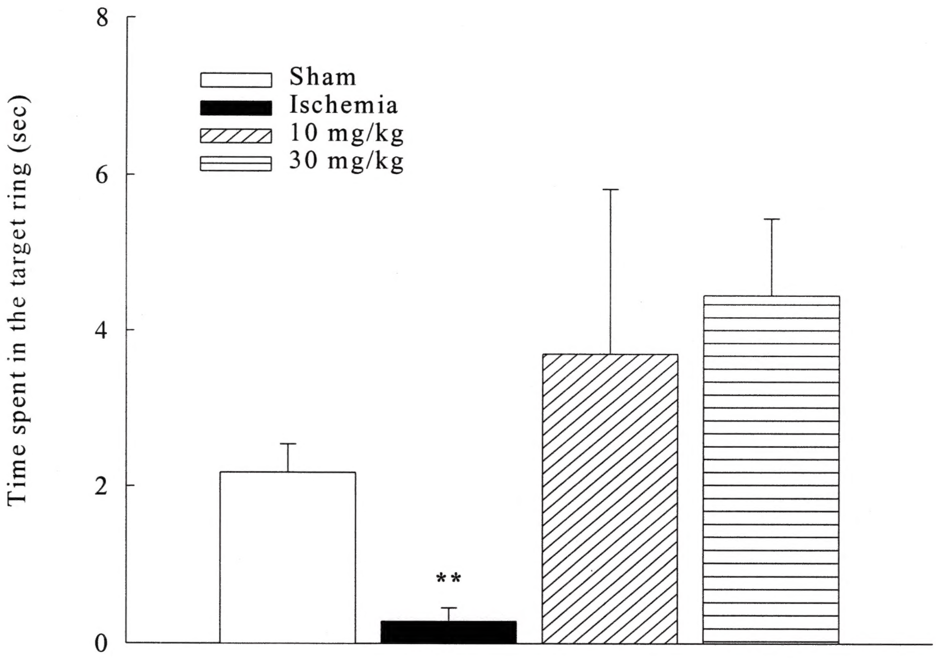
   （Tanaka et al., Eur J Pharmacol 1998）



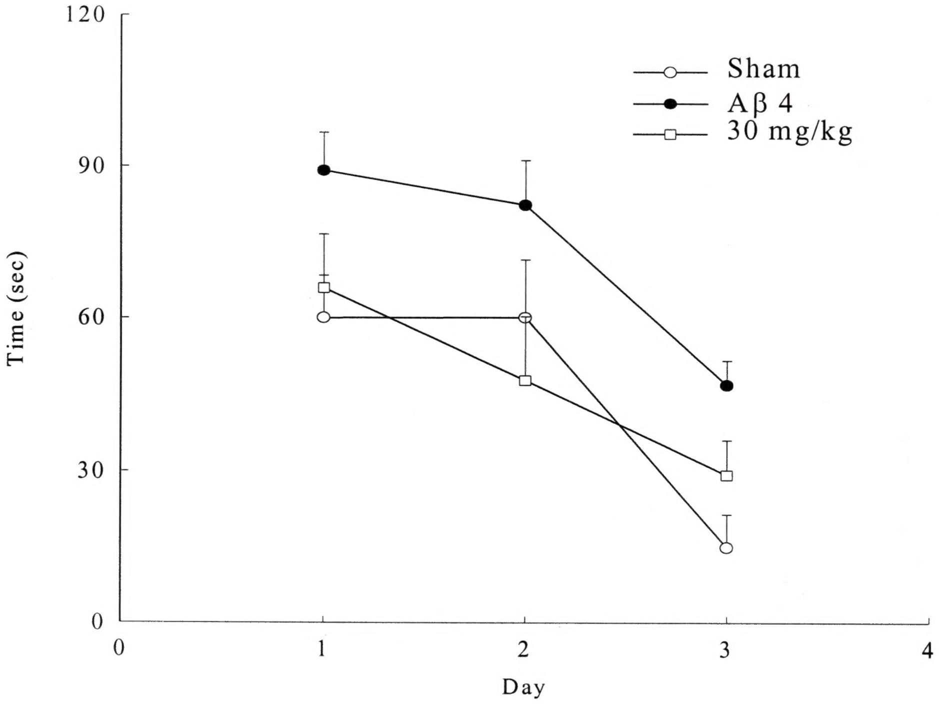
This slide shows that butanolic and water layer of *Rehmannia glutinosa* attenuated the impairment of passive avoidance performance in ischemia rats.



This slide shows that butanolic layer of *Rehmannia glutinosa* at 30 mg/kg attenuated the impairment of water maze performance on 3 consecutive training days in ischemia rats.



This slide shows that butanolic layer of *Rehmannia glutinosa* at 10 and 30 mg/kg attenuated the impairment of reference memory on 4 hours after 3 consecutive training days in ischemia rats.



This slide shows that butanolic layer of *Rehmannia glutinosa* at 30 mg/kg attenuated the impairment of water maze performance induced by amyloid β peptide (1-40).

Conclusion

1、Crude extract and butanolic layer of ***Rehmannia glutinosa*** facilitated the passive avoidance and water maze performance

2、Butanolic layer of ***Rehmannia glutinosa*** attenuated the impairment of passive avoidance and water maze performance induced by **carotid artery occlusion** or **amyloid β peptide (1-40).**